IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

NIPPON SHINYAKU CO., LTD., Plaintiff, v. SAREPTA THERAPEUTICS, INC., Defendant.	C.A. No. 21-1015 (GBW) **DEMAND FOR JURY TRIAL**
SAREPTA THERAPEUTICS, INC. and THE UNIVERSITY OF WESTERN AUSTRALIA, Defendant/Counter-Plaintiffs, v. NIPPON SHINYAKU CO., LTD. and NS PHARMA, INC., Plaintiff/Counter-Defendants.	[redacted] [redacted]

NS'S MEMORANDUM OF LAW IN SUPPORT OF ITS MOTION FOR PARTIAL SUMMARY JUDGMENT NO. 1 REGARDING INVALIDITY OF THE UWA PATENTS

Amanda S. Williamson (admitted *pro hac vice*)
Christopher J. Betti (admitted *pro hac* vice)
Krista V. Venegas (admitted *pro hac* vice)
Wan-Shon Lo (admitted *pro hac vice*)
Maria E. Doukas (admitted *pro hac vice*)
Zachary Miller (admitted *pro hac vice*)
Guylaine Haché (admitted *pro hac vice*)
Michael T. Sikora (admitted *pro hac vice*)
110 N. Wacker Drive, Suite 2800
Chicago, IL 60601
Telephone: 312.324.1000 | Fax: 312.324.1001
amanda.williamson@morganlewis.com
christopher.betti@morganlewis.com
krista.venegas@morganlewis.com
shon.lo@morganlewis.com
maria.doukas@morganlewis.com
zachary.miller@morganlewis.com
guylaine.hache@morganlewis.com
michael.sikora@morganlewis.com

Amy M. Dudash (DE Bar No. 5741)
MORGAN, LEWIS & BOCKIUS LLP
1201 N. Market Street, Suite 2201
Wilmington, DE 19801
Telephone: 302.574.3000 | Fax: 302.574.3001
amy.dudash@morganlewis.com

Alison P. Patitucci (admitted *pro hac vice*)
2222 Market Street
Philadelphia, PA 19103
Telephone: 215.693.5000 | Fax: 215.963.5001
alison.patitucci@morganlewis.com

Attorneys for Plaintiff/Counterclaim Defendant Nippon Shinyaku Co., Ltd. and Counterclaim Defendant NS Pharma, Inc.

Dated: December 11, 2023

TABLE OF CONTENTS

Page

TABLE OF AUTHORITIES

Page(s)

Cases

Statutes

TABLE OF ABBREVIATIONS

’007 Interference	Leiden University Medical Centre in Interference No. 106,007
’590 Patent	U.S. Patent No. 10,227,590
’827 Patent	U.S. Patent No. 10,266,827
’851 Patent	U.S. Patent No. 9,994,851
2’OMe	2 ' - O - Methyl Phosphorothioate
AO	Antisense Oligonucleotide
DMD	Duchene Muscular Dystrophy
Dowdy Opening	Opening Report of Steven F. Dowdy, Ph.D. dated September 7, 2023
Dowdy Rebuttal	Rebuttal Report of Steven F. Dowdy, Ph.D. dated October 11, 2023
Dowdy Dep.	Deposition Transcript for Dr. Steven Dowdy, November 8, 2023
Hasting Opening	Expert Report of Dr. Michele L. Hastings Regarding Invalidity of the UWA Patents dated September 8, 2023
IPR	*Inter Partes* Review
Nelson Opening	Opening Expert Report of Stanley Nelson, M.D. dated September 6, 2023
Nippon Shinyaku	Nippon Shinyaku Co., Ltd
NSP	NS Pharma, Inc.
NS Patents	U.S. Patent Nos. 9,708,361, 10,385,092, 10,407,461, 10,487,106, 10,647,741, 10,662,217, 10,683,322
Patent Office	United States Patent and Trademark Office
PMO	Phosphorodiamidate Morpholino Oligomer
POSA	Person of Ordinary Skill in the Art

Sarepta Therapeutics	Sarepta Therapeutics, Inc.
SEQ ID NO. 195	AO with sequence "CUG AAG GUG UUC UUG UAC UUC AUC C" targeting positions +23+47 of the human dystrophin pre-mRNA
SOF	Conscise Statement of Facts in Support of NS's Motion for Partial Summary Judgment No. 1 Regarding Invalidity of the UWA Patents
UWA	The University of Western Australia
UWA Patents	U.S. Patent Nos. 9,994,851, 10,227,590, and 10,266,827
VILTEPSO	VILTEPSO®
VYONDYS 53	VYONDYS 53®

I. INTRODUCTION

The Court should grant summary judgment in favor of Plaintiff/Counter-Defendant Nippon Shinyaku and Counter-Defendant NSP, (collectively, "NS") and find that the UWA Patents asserted by Defendants and Counter-plaintiffs Sarepta and UWA (collectively, "Sarepta") are invalid (D.I. 86, Claim II and D.I. 96, Second Defense). The UWA Patents' claims are directed to a genus of AOs (molecules that include chains of nucleotides) that bind to and induce skipping of exon 53 of human dystrophin pre-mRNA and that can be used for the treatment of DMD. Viewed in the light most favorable to Sarepta, the UWA Patents describe, at most, only a single AO that falls within their very broadly claimed genus and provide no disclosure explaining how an AO's structure correlates to the claimed function of exon 53 skipping. Precedent is clear: one example lacking explanation of any correlation between AO structure and exon 53-skipping function cannot provide written description for a broadly claimed functional genus. Likewise, no reasonable jury could conclude that the UWA Patents' scant disclosure describes or enables AOs across the claimed genus's full scope.

II. NATURE AND STAGE OF THE PROCEEDINGS

NS initiated this action on July 13, 2021 asserting claims against Sarepta for patent infringement of the NS Patents, declaratory judgment of invalidity of the UWA Patents, and breach of contract. D.I. 2. On January 28, 2022, Sarepta filed its answer and asserted counterclaims, including for infringement of the UWA Patents and declaratory judgment of invalidity for the NS Patents. D.I. 89. On August 16, 2023, NS filed an amended answer and counterclaims, including for unenforceability of the UWA Patents due to inequitable conduct and *Walker Process* fraud claims. D.I. 324. On September 1, 2023, Sarepta filed an amended answer and counterclaims, including for unenforceability of the NS Patents due to inequitable conduct. D.I. 344. Fact and expert discovery are now closed, and trial is set for May 13, 2024. *See* D.I. 269 at 2.

III. CONCISE STATEMENT OF FACTS

NS incorporates by reference its contemporaneously filed concise statement of facts.

IV. THE PARTIES AND THEIR ASSERTED PATENTS AND PRODUCTS

Nippon Shinyaku is an innovative pharmaceutical company whose mission is to "help people lead healthier, happier lives." D.I. 86 ¶ 5. It accomplishes this mission by developing and supplying unique and high-quality therapies. *Id*. One such therapy is VILTEPSO, an AO used to treat DMD patients amenable to exon 53 skipping. D.I. 39 ¶¶ 36-38. DMD is a devastating form of muscular dystrophy caused by a lack of functional dystrophin—a protein that maintains the integrity of muscle fibers. Ex. 1 (Dowdy Opening) ¶ 69. DMD patients lack functional dystrophin because the dystrophin gene contains mutations that disrupt protein translation. Ex. 1 (Dowdy Opening) ¶ 71. In the context of DMD, AOs (which include a chain of nucleotides) are designed to "skip" the targeted exon, resulting in production of a truncated but still functional dystrophin protein. Ex. 1 (Dowdy Opening) ¶ 76.

The active ingredient of NS's VILTEPSO is viltolarsen, an AO that is 21 nucleobases in length and targets positions +36+56 of exon 53 of the dystrophin pre-mRNA. D.I. 86 ¶ 36; D.I. 89 ¶ 53. Sarepta accuses VILTEPSO of infringing the UWA Patents. D.I. 89 ¶¶ 35-73. Sarepta also markets and sells an AO used to treat DMD patients amenable to exon 53 skipping, VYONDYS 53. Ex. 12 (Nelson Opening) ¶¶ 33, 68. The active ingredient in VYONDYS 53 is golodirsen, an AO that is 25 bases in length and targets positions +36+60 of exon 53 of the dystrophin pre-mRNA. Ex. 1 (Dowdy Opening) ¶ 128.

The UWA Patents broadly claim a functional genus of AOs that induce exon 53 skipping. A representative claim is as follows:

> 1. An **antisense oligonucleotide** of **20 to 31 bases** comprising **a base sequence that is 100% complementary to consecutive bases** of a target region of exon 53 of the human dystrophin pre-mRNA, **wherein the base sequence comprises at**

> **least 12 consecutive bases of CUG AAG GUG UUC UUG UAC UUC AUC C (SEQ ID NO: 195)**, in which uracil bases are thymine bases, wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide, and wherein the antisense oligonucleotide **induces exon 53 skipping**; or a pharmaceutically acceptable salt thereof.

D.I. 2, Ex. J. '590 Patent claim 1.[1] NS's expert, Dr. Michele Hastings, has calculated the number of potential **candidate AOs falling within this genus** as in the **many trillions**. SOF ¶ 5.

V. SUMMARY OF THE ARGUMENT

The Court should grant summary judgment in NS's favor because:

1. The UWA Patents are invalid for lack of written description. The UWA Patents claim vast functional genera of AOs in a highly unpredictable field (AOs that induce exon 53 skipping). Yet, the specification discloses, at best, a single candidate meeting the claims' structural limitations and further fails to disclose any common structural features that would allow a POSA to distinguish functional AOs, *i.e.*, AOs that induce exon 53 skipping, from those that do not absent extensive, iterative trial-and-error experimentation. As such, the UWA Patents' disclosure fails to provide sufficient written description as a matter law. *Juno Therapeutics, Inc. v. Kite Pharma, Inc.,* 10 F.4th 1330, 1342 (Fed. Cir. 2021).

2. The UWA Patents are also invalid for lack of enablement because the UWA Patents' scant disclosure likewise does not enable the genus's full scope. Rather, the specification leaves POSAs with a "research assignment[]" to recreate the inventors' "own trial-and-error method for finding functional [AOs]" from the vast numbers of candidate AOs, which fails the enablement requirement as a matter of law. *Amgen Inc. v. Sanofi*, 598 U.S. 594, 614 (2023).

[1] Emphasis added when not otherwise indicated.

VI. LEGAL STANDARD

Summary judgment is "'put up or shut up' time for the non-moving party." *Berckeley Inv. Grp., Ltd. v. Colkitt*, 455 F.3d 195, 201 (3d Cir. 2006). The movant's burden is "discharged by pointing out … that there is an absence of evidence supporting the non-moving party's case." *Tri-State Energy Sols., LLP v. KVAR Energy Sav. Inc.*, 845 F. Supp. 2d 615, 618 (D. Del. 2012). The non-movant "must rebut the motion with facts in the record and cannot rest solely on assertions made in the pleadings, legal memoranda, or oral argument." *Berckeley*, 455 F.3d at 201. "The mere existence of a scintilla of evidence in support of the plaintiff's position will be insufficient; there must be evidence on which the jury could reasonably find for the plaintiff." *Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 252 (1986).

VII. ARGUMENT

A. The UWA Patents are Invalid for Lack of Written Description.

A patent's specification must "reasonably convey[] to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." *Ariad Pharm. Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc). "[T]he hallmark of written description is disclosure." *Id.* "When a patent claims a genus using functional language to define a desired result, 'the specification must demonstrate that the applicant has made a generic invention that achieves the claimed result.'"[2] *AbbVie Deutschland GmbH & Co., KG v. Janseen Biotech, Inc.*, 759 F.3d 1285, 1299 (Fed. Cir. 2014) (quoting *Ariad*, 598 F.3d at 1349). "**[W]ritten description of a broad genus requires description not only of the outer limits** of the genus **but also of either a representative number of members** of the genus or **structural features**

[2] This requirement applies equally to the '827 Patent's method claims. *Univ. of Rochester v. G.D. Searle & Co., Inc.*, 358 F.3d 916, 929 (Fed. Cir. 2004) ("Regardless whether a compound is claimed *per se* or a method is claimed that entails the use of the compound, the inventor cannot lay claim to that subject matter unless he can provide a description of the compound . . . .").

common to the members of the genus, in either case with enough precision that a relevant artisan can visualize or recognize the members of the genus." *Regents of Univ. of Minnesota v. Gilead Scis., Inc.*, 61 F.4th 1350, 1356 (Fed. Cir. 2023) (citing *Ariad*, 598 F.3d at 1350-52).

The UWA Patents fail to disclose either a representative number of species or a common structural feature. They **disclose**, at most, **only one AO species—a PMO version of SEQ ID NO. 195—that could satisfy the claims' structural requirements** of having 20 to 31 bases, 12 consecutive bases of SEQ ID NO. 195, and PMO chemistry as well as the claims' functional requirement to induce exon 53 skipping. One disclosed species cannot provide written descriptive support for a broad, functional genus. *See, e.g.*, *Juno Therapeutics, Inc. v. Kite Pharma, Inc.*, 10 F.4th 1330, 1340-42 (Fed. Cir. 2021) (no written description where patent "discloses only one CD19-specific scFv" but claimed a "genus of functional CD19-specific scFvs.").

The UWA Patents also fail to disclose a structure-function correlation. As the Federal Circuit explained in *Idenix Pharmaceuticals LLC v. Gilead Sciences Inc.*, "[i]n the absence of that guidance [into what compounds beyond the examples and formulas, if any, would provide the same result], the listed examples and formulas cannot provide adequate written description support for undisclosed [species]." 941 F.3d 1149, 1164 (Fed. Cir. 2019).

At most, the UWA Patents provide examples of four AOs that induce exon 53 skipping individually, only one of which—SEQ ID NO 195—could potentially fall within the scope of the claimed genus without any further guidance as to how their structure or sequence correlates to exon 53 skipping or how or why those examples might be predictive of exon 53 skipping in AOs not disclosed in the UWA Patents. SOF ¶ 3. Merely disclosing examples without explanation and guidance cannot provide written description for the UWA Patents' broadly claimed genus.

i. The UWA Patents do not Disclose Representative Species Falling Within the Scope of the Claimed Genus.

To demonstrate possession of a genus through "a representative number of species falling within the scope of the genus," the specification must "describ[e] a variety of materials constituting the genus." *Ariad*, 598 F.3d at 1350. "[M]erely drawing a fence around the outer limits of a purported genus is not an adequate substitute." *Id*. As the Federal Circuit has explained, "relatively few representative examples" do not suffice where, as here, "tens or hundreds of thousands of possible" structural candidates exist, and yet "the [accused product] is conspicuously absent." *Idenix*, 941 F.3d at 1165. Here, it is undisputed that the UWA Patents lack any disclosure of AOs with the same nucleobase sequences as either the accused product, NS's VILTEPSO or Sarepta's product, VYONDYS 53. SOF ¶ 2. Moreover, where, as here, "the art is unpredictable … disclosure of more species is necessary to adequately show possession of the entire genus." *Synthes USA, LLC v. Spinal Kinectics, Inc.*, 734 F.3d 1332, 1344 (Fed. Cir. 2013).

The UWA Patents' broadly claimed genus casts a very wide net potentially encompassing at least tens of thousands, if not millions or trillions, of candidate AOs, including NS's VILTESPO. The UWA Patents' disclosure of a single potential species—SEQ ID NO. 195—in the unpredictable field of AOs that induce exon 53 skipping is insufficient to provide written description support for such a broadly claimed genus.

a. The Field of Exon 53 Skipping AOs was and Remains Highly Unpredictable.

There is no genuine dispute that the field of exon skipping is highly unpredictable further necessitating a robust disclosure to satisfy the written description requirements. *See Synthes*, 734 F.3d at 1344. Sarepta made repeated representations to the Patent Office during the '851 Patent's prosecution and '007 Interference (an invalidity proceeding to which UWA was a party) affirming and relying on high levels of unpredictability in the field of exon 53-skipping AOs to obtain its

patent and invalidate the patent of another party. *See* SOF ¶¶ 10-13, 15. For example, during the '007 Interference, Sarepta argued that "[redacted]" and that there is "[redacted]" SOF ¶ 12. Similarly, during prosecution of its patents, Sarepta presented examples from other researchers to demonstrate that exon 53 skipping was unpredictable as of 2005 and remained unpredictable many years later, citing, as one example, a 2011 publication as evidence that "**selecting specific antisense oligonucleotide sequences to induce effective dystrophin exon skipping remains an unpredictable exercise**." SOF ¶ 11.

These and Sarepta's other **statements are**, at the very least, party admissions. Because Sarepta made them during prosecution, the admissions are **binding**. *See, e.g.*, *Sherwin-Williams Co. v. PPG Indus., Inc.*, No. 17-1023, 2021 WL 211497, at *3 (W.D. Pa. Jan. 21, 2021); *see also Procter & Gamble Co. v. Nabisco Brands, Inc.*, 711 F. Supp. 759, 770 (D. Del. 1989). Given that Sarepta's arguments successfully induced the Patent Office to both issue the UWA Patents and invalidate another parties' exon 53-directed claims, judicial estoppel also precludes Sarepta from now contesting that the art was "highly unpredictable." *MobileMedia Ideas, LLC v. Apple Inc.*, 907 F. Supp. 2d 570, 623 (D. Del. 2012), *vacated in part*, 780 F.3d 1159 (Fed. Cir. 2015).

The evidence here also includes the underlying evidence Sarepta relied upon and expert testimony in this case affirms that the "highly unpredictable" nature of exon 53-skipping AOs existed at the UWA Patents' priority date and remains to this day. *See, e.g.*, SOF ¶¶ 10-13, 15; D.I. 313, Ex. 5 ¶¶ 68-86; Ex. 5 (Hastings Opening) ¶¶ 116-117; Ex. 13 (Dowdy Dep.) at 209:19-

23,192:1-4. Thus, there is no dispute that the field of exon 53 skipping AOs was unpredictable at the time of the invention and remains so.

b. The UWA Patents Claim a Vast Genus.

There is no genuine dispute that the UWA Patents' broadly claimed functional genus is vast. NS's expert, Dr. Michele Hastings, [redacted]. SOF ¶ 5. Sarepta's expert, Dr. Steven Dowdy, [redacted]. SOF ¶¶ 6-9. Sarepta does not dispute Dr. Hastings's methodology in coming to her calculation. SOF ¶ 5. Rather, Sarepta, through its expert, Dr. Dowdy, argues that Dr. Hastings's calculation is overly broad because it [redacted]."[3] SOF ¶¶ 5-6.

Even if considered, Dr. Dowdy's testimony does not create any genuine dispute because, even under his improper construction, the claimed genus remains very broad. As in *Idenix*, "the structural limitations still encompass **[at least] some number of thousands** of compounds" **in the patentee's "best case"** and was considered broad. *Idenix Pharms. LLC v. Gilead Scis. Inc.*, 941 F.3d 1149, 1157-58 (Fed. Cir. 2019) (crediting "meticulous[] calculat[ion]" of "more than 7,000 unique configurations"). The UWA Patents' potential genera remain large by any measure and thus require far more support than the disclosure of a single species—SEQ ID NO. 195.[4]

[3] As set forth in NS's currently filed *Daubert* Motion to Exclude the Testimony and Opinions of Steven F. Dowdy, Dr. Dowdy relies upon an incorrect construction in his attempts to rebut Dr. Hastings's calculation of the UWA Patents' claimed genera. Because Dr. Dowdy's opinion is based on an incorrect construction, it cannot create a genuine issue of material fact as to the size of the genera at issue. *EMC Corp. v. Pure Storage, Inc.*, 154 F. Supp. 3d. 81, 98-99 (D. Del. 2016).

[redacted]

c. UWA Patents' Single Disclosed Species is not Representative of its Vast and Broadly Claimed Genus.

The UWA Patents undisputedly describe, at best, only a single AO that potentially falls with the claimed genus—a PMO version of SEQ ID NO. 195. *See* D.I. 2, Ex. I tbls. 1, 39. SEQ ID NO. 195 is a 25-base AO, targets position +23+47, contains 25 consecutive bases of itself, and purportedly demonstrated "[v]ery faint skipping to 50 nM." SOF ¶ 2.[5]

For the UWA Patents' claims, Sarepta started with SEQ ID NO. 195 and used structural limitations of AO length—20-31 bases—and overlap of base sequence—at least 12 bases of overlap and up to 25 bases of overlap with SEQ ID NO. 195—to extend its claims out well beyond that which it discovered. *See e.g.* D.I. 2, Ex. I cl. 1. However, the UWA Patents provide no written description support for the claimed expansion beyond SEQ ID NO. 195. The UWA Patents do not disclose a single AO of 20, 22, 23, 26, 28, 29 or 30 bases in length that induces exon 53 skipping. SOF ¶ 3. Nor do the UWA Patents provide any data demonstrating that a 12-base AO could induce exon 53 skipping, let alone data demonstrating that a 12-base portion of SEQ ID NO. 195 could induce exon 53 skipping. SOF ¶ 3; Ex. 5 (Hastings Opening) ¶¶ 50-53.

These limitations originated from the prosecuting attorney's resort to specification sections regarding other exons, including exon 19. Ex. 16 (Mandragouras Dep.) at 55:13-57:8. But, both parties' experts agree that disclosures for AOs targeting other exons are not predictive of exon 53

[redacted] SOF ¶¶ 6-7. [redacted] SOF ¶¶ 6-9.

[5] Notably, SEQ ID NO. 195 has a different chemical backbone than the PMO backbone required by the asserted claims, and itself is not a candidate species. Rather, Sarepta relies on a PMO analog it contends is disclosed (without any exon skipping data) in Table 1a of the UWA Patents. SOF ¶¶ 2-3; *see also* Ex. 5 (Hasting Opening) ¶ 50.

skipping activity (SOF ¶ 4; Ex. 13 (Dowdy Dep.) at 50:13-51:11; Ex. 5 (Hastings Opening) ¶¶ 52-53) and thus cannot provide written description support for exon 53-skipping AOs. For this reason alone, the claims should be found invalid for lack of written description.

A comparison of the disclosed species—SEQ ID NO. 195—and non-disclosed but potentially ensnared AO's, *i.e.*, NS's VILTEPSO and Sarepta's VYONDYS 53, demonstrates the overreach inherent in the UWA Patents' broadly claimed genus. [redacted].

[redacted]

[redacted] "ha[ve] not described the genus sufficiently to show that the inventor invented, or had possession of, the genus. He only described a portion of it." *AbbVie*, 759 F.3d at 1300; *see also Enzo Biochem, Inc. v. Gen-Probe Inc.*, 323 F.3d 956, 967 (Fed. Cir. 2002) (specification's lack of "a sufficient number of species" meant that it failed to show "that the inventors had made a generic invention, *i.e.*, that they had **possession of the breadth of the genus**, as opposed to merely one or two such species"); *Regents of the Univ. of California v. Eli Lilly & Co.*, 119 F.3d 1559, 1567-68 (Fed. Cir. 1997) (holding claims to a broad genus of genetic material invalid because the specification disclosed only one particular species). The lack of disclosure is particularly acute here where the field is unpredictable and "disclosure of more species is necessary to adequately show possession of the entire genus." *Synthes*, 734 F.3d at 1344.

ii. The UWA Patents do not Disclose Common Structural Features or Structural Correlation to the Claimed Exon 53-Skipping Function.

The UWA Patents also lack written description and are invalid because they fail to provide any disclosure of "common structural features of the claimed [] genus" that "identify which [candidates] would function as claimed." *Juno*, 10 F.4th at 1336. *see also AbbVie*, 759 F.3d at 1301 (explaining it is "difficult to establish" the necessary "structure-function correlation" when the art is "highly unpredictable," leaving functional genus claims "inherently vulnerable to … lack of written description support").

a. The Claimed Genus Includes Species That do not Share Common Structural Features.

The UWA Patents fail to disclose any structure-function correlation between the claims' structural limitations and exon 53 skipping. The UWA Patents list only the exon 53-skipping results without further explanation and fail to explain what makes the example AOs effective, or why they induce exon 53 skipping when other do not. *See, e.g.*, D.I. 2, Ex. I at 64:32-65:67. The

specification provides **no discussion whatsoever** about why particular exon 53-directed AOs worked, what structural characteristics of those exon 53-directed AOs the inventors believed to be driving that exon 53-skipping function, or what future AOs they expected to also induce exon 53-skipping. *Id.* The it fails to allow a POSA to visualize the full scope of the claimed genus.

The UWA Patents' claims also lack written description because they do not share "common" base sequences. The recited "base sequence" need only comprise 12 consecutive bases of SEQ ID NO. 195—*i.e.*, less than **half** of its 25 bases, such that claimed AOs may have entirely discrete, non-overlapping "base sequences" that "comprise at least 12 consecutive bases of SEQ ID NO. 195." Ex. 5 (Hastings Opening) ¶¶ 56-65. NS's expert, Dr. Hastings, [redacted] Because AOs within the genus lack a common base sequence, it is impossible to determine which, if any, common bases sequences could be contributing to the claimed exon 53-skipping function.

b. Sarepta's Purported "Hot Spot" Does Not Support any Structure Function Correlation.

Sarepta, through it expert, Dr. Dowdy, tries to recharacterize the UWA Patents as disclosing a "hot spot" [redacted].[6] *See, e.g.*, Ex. 3 (Dowdy Reply) ¶ 67. Sarepta's purported "hot spot" cannot establish any structure-function correlation for the AOs falling within the claimed genus because many of the AOs that would target the "hot spot" are not in claimed genus. Thus, their structure is irrelevant to determining a structure-function correlations for candidate AOs that actually may fall within the claimed genus. [redacted]. Ex. 3 (Dowdy Reply) ¶ 67. These examples and results are provided without explanation, let alone explanation as to whether and why AOs binding at or near the so-called "hot spot" induce exon 53 skipping. *See e.g.,* D.I. 2-9, Ex. I ('851 Patent) at 64:32-65:67. Such barebones listings of examples and results does not demonstrate structure-function correlation. *Idenix* 941 F.3d at 1165 ("In the absence of that guidance, the listed examples and formulas cannot provide adequate written description support for undisclosed [species].")

The Federal Circuit's decisions in *Juno* and *Idenix* are instructive. In *Juno*, finding claims to a functionally claimed genus of antibodies invalid for failure to comply with written description, it was irrelevant that "scFvs in general were well-known or have the same general structure"—the specification "disclose[d] only two scFv examples and provide[d] no details regarding the

[6] NS disagrees that a POSA would view the UWA Patents as identifying a "hot spot" but, for purposes of this motion only, accepts Dr. Dowdy's opinion.

characteristics, sequences, or structures that would allow" a POSA "to determine which scFvs" had the claimed functionality." 10 F.4th at 1339-40. And in *Idenix*, the specification's disclosure contained far more than the single-disclosed species and three unclaimed examples [redacted]—it provided "lists or examples of supposedly effective nucleosides." 941 F.3d at 1664. But even that disclosure was insufficient without "explain[ing] what makes the [examples] effective, or why." *Id.* "As a result, a POSA is deprived of any meaningful guidance into what compounds beyond the examples and formulas, if any, would provide the same result." *Id.*

Even if the UWA Patents are directing POSAs to a "hot spot" region in which it would be obvious to experiment further to find sequences that have exon skipping activity, such a starting point does not demonstrate possession of a genus encompassing every species eventually found therein. "[T]he hallmark of written description is disclosure." *Ariad*, 598 F.3d at 1351. "It is not enough that a claimed invention is 'an obvious variant of that which is disclosed in the specification.'" *Novartis Pharms. Corp. v. Accord Healthcare, Inc.*, 38 F.4th 1013, 1016 (Fed. Cir. 2022), *cert. denied sub nom. Novartis Pharms. Corp. v. HEC Pharm. Co.*, 143 S. Ct. 1748 (2023).

[redacted]. SOF ¶ 14. Consequently, Dr. Dowdy's purported "hot spot" is nothing more than "[a] mere wish or plan for obtaining the claimed invention" and cannot provide written description for the UWA Patents' vast genus. *Juno*, 10 F.4th at 1335 (citation and internal quotes omitted).

c. There is no Correlation Between the UWA Patents' Claimed Structure and Exon 53-Skipping Functionality.

In any event, no structure-function correlation exists. NS's expert, Dr. Hastings, [redacted]

[redacted] Thus, the record evidence establishes that neither the claimed 12 bases of SEQ ID NO. 195 nor binding at the "hot spot" provide any assurance that a given PMO will exhibit the claimed functionality. Again, exon 53-skipping functionality is something that needs to be established empirically. SOF ¶ 14.

B. The UWA Patents are Also Invalid for Lack of Enablement.

The UWA Patents lack enablement as a matter of law. "In unpredictable art areas, [the Federal Circuit] has refused to find broad generic claims enabled by specifications that demonstrate the enablement of **only one or a few embodiments** and do not demonstrate with reasonable specificity how to make and use other potential embodiments **across the full scope of the claim."** *PPG Indus., Inc. v. Guardian Indus. Corp.*, 75 F.3d 1558, 1564 (Fed. Cir. 1996); *see also ALZA Corp.*, 603 F.3d 935, 941 (Fed. Cir. 2010); *Enzo Biochem, Inc. v. Calgene, Inc.*, 188 F.3d 1362, 1377 (Fed. Cir. 1999) (affirming finding that "antisense was highly unpredictable" and resulting judgment of non-enablement). To provide sufficient enablement, a specification must "describe the invention 'in such full, clear, concise, and exact terms as to enable any person skilled in the art' to 'make and use' the invention." *Amgen*, 598 U.S. at 612 (quoting 35 U.S.C. § 112(a)). "A claim is not enabled when, 'at the effective filing date of the patent, one of ordinary skill in the art could not practice their full scope without undue experimentation.'" *Idenix*, 941 F.3d at 1154

(quoting *Wyeth & Cordis Corp. v. Abbott Lab'ys,* 720 F.3d 1380, 1384 (Fed. Cir. 2013)). "Enablement is a question of law based on underlying factual findings." *Baxalta Inc. v. Genentech, Inc.*, 81 F.4th 1362, 1365 (Fed. Cir. 2023).

Enablement requires more than simply providing POSAs a "research assignment[]" to "create a wide range of candidate[s]" and "then screen each to see which happen to" have the claimed functionality. *Amgen*, 598 U.S. at 614. A mere "starting point" from which POSAs must "engage in an iterative, trial-and-error process to practice the claimed invention," as presented by the UWA Patents, is not enabling. *Wyeth*, 720 F.3d at 1386. The Court should therefore hold the UWA Patents invalid as non-enabled.

i. There Is No Genuine Dispute that Practicing the Full Scope of the Claims Would Require Extensive Trial-and-Error Experimentation.

As discussed above, *supra* Section VII.A.i.b., there is no genuine dispute of fact that the asserted claims broadly encompass at least many tens of thousands (if not many trillions) of candidate AOs that meet the claims' structural limitations. There likewise is no genuine dispute that the art was highly unpredictable at the time of the UWA Patents' claimed priority date. *Supra* Section VII.A.i.a. As the UWA Patents explain, this unpredictability necessitates extensive trial-and-error experimentation to identify AOs that induce the claimed exon 53 skipping functionality. D.I. 2-9, Ex. I ('851 Patent) at 24:4-12.

To identify AOs that induce the claimed exon 53 skipping, a POSA must empirically test each AO to determine whether it induces exon skipping. SOF ¶ 10-15. Even Sarepta's expert, Dr. Dowdy, [redacted]. SOF ¶ 14. The need to iteratively test AO candidates is particularly acute for AOs that, in whole or in part, are not 100% complementary to the dystrophin pre-mRNA: [redacted]

[redacted][7] *Id.* [redacted] Ex. 13 (Dowdy Dep.) at 24:9-25:19. [redacted] *Id.*; *see also id.* at 30:23-31:14 ([redacted]).

These admissions squarely align with Sarepta's representations to the Patent Office as set forth in Section VII.A.1.a above. According to Sarepta, "[i]n this unpredictable field, [] **each AO[] needs to be empirically tested**." SOF ¶ 12. *Id.* Even in 2009, data published "show[ed] the complex interactions between nucleotide length, nucleotide sequence, internucleotide linkages, and chemical backbone, and reinforces the **need for empirically testing each chemically distinct AO[]"** and that "Short of **empirically testing each AO[]**, a skilled person would have **no way of knowing whether a particular AO[] would be capable of inducing skipping of exon 53**." UWA Motion 1 at 6, 19. Sarepta cannot now be heard to argue otherwise.

On this record, a reasonable jury could only find that practicing the full scope of each claimed genus requires synthesizing and screening at least many thousands if not millions or trillions of candidate AOs for exon 53 skipping. The Federal Circuit has repeatedly held that this constitutes undue experimentation. In *Wyeth*, the genus encompassed "at least tens of thousands of candidate compounds" and it was "necessary [for a POSA] to first synthesize and then screen

[7] Under the claim construction issued by the Court and applied by Dr. Hastings, AOs falling within the claimed genus an include up to 19 mismatched bases. SOF ¶ 8. Even if Dr. Dowdy's newly offered construction [redacted] the genus would include AOs with at least 2 and possibly up to 4 mismatched bases. SOF ¶¶ 5-8.

each candidate compound" to determine whether it exhibited the claimed "functional effects." 720 F.3d at 1384-86. "Notwithstanding the fact that screening an individual compound for effectiveness was considered 'routine,' [the Federal Circuit] concluded as a matter of law in *Wyeth* that the claim was not enabled." *Idenix*, 941 F.3d at 1163. The Federal Circuit held that this "principle controls" in *Idenix*. There, as here, "[a] reasonable jury could only have concluded that there were at least many, many thousands of candidate compounds, many of which would require synthesis and each of which would require screening." *Id.* "That constitutes undue experimentation." *Id.*

ii. The Specification's Meager Guidance Does Not Eliminate the Need for Onerous Trial-and-Error Experimentation.

Nothing in the UWA Patents' disclosure obviates the need for a POSA to iteratively screen each candidate AO for exon-skipping activity.

The specification discloses, at best, only "[a] single member of the genus" within the scope of the asserted claims ([redacted]) and provides no explanation as to why this sole member of the genus purportedly generated "very weak skipping." D.I. 2-9, Ex. I ('851 Patent) 64:32-65:67. It likewise only generically describes the screening methodology used by the UWA researchers in their work. *Id*. (mentioning general steps for screening AOs for functionality but providing no details regarding reagents used and the methodology at each step). [redacted] Ex. 13 (Dowdy Dep.) at 98:15-100:1 ("[redacted]"); Ex. 1 (Dowdy Opening) ¶¶ 640-641.) And the UWA Patents provide no explanation regarding why particular exon 53-directed AOs worked, what structures in those exon 53-directed AOs the inventors believed to be driving that exon 53-skipping

function, nor what future AOs they expected to also induce exon 53-skipping. D.I. 2-9, Ex. I (''851 Patent) at 64:32-65:67.

This scant guidance on sequences to test or what test conditions were used and single example within the scope of the claims that lead to some skipping activity do not constitute enablement, particularly given the claims' breadth and unpredictability inherent in exon 53-skipping AOs. "An enabling disclosure must 'be commensurate in scope with the claim.'" *Idenix*, 941 F.3d at 1160 (quoting *In re Hyatt*, 708 F.2d 712, 714 (Fed. Cir. 1983)). Each claim "requires more than just an identification of [an AO with at least 12 consecutive bases of SEQ ID NO. 195]: it requires identification of which [AOs with such bases] will effectively" induce skipping of exon 53." *Id.* "Without specific guidance on that point, the specification provides 'only a starting point, a direction for further research." *Id.* (quoting *ALZA Corp.*, 603 F.3d at 941.

In fact, compared to various other patents courts have held non-enabled, the UWA Patents disclose markedly **less** guidance. In *Idenix*, the specification "contained data showing working examples of 2'-methl-up nucleosides with [the claimed] efficacy against HCV," but those "**four examples** … [we]re insufficient to support enablement." *Idenix*, 941 F.3d at 1161. In *Baxalta*, "the written description disclose[d] the amino acid sequences for only **eleven antibodies** with the two claimed functions." *Baxalta*, 81 F.4th at 1366. And in *Amgen*, the specification "identified the amino acid sequences of **26 antibodies** that perform these two functions, and it depicted the three-dimensional structures of two of these 26 antibodies." 598 U.S. at 602-03.

The fundamental defect here is the same. If a POSA wishes to practice the full scope of the UWA Patents, their only choice is to systematically evaluate candidate AOs through trial-and-error screening. To the extent that Sarepta contends the specification directed POSAs to a purported binding "hot spot" on the target pre-mRNA to help identify potential AO sequences that

may lead to exon 53 skipping, Sarepta falls far short of the requirements for enablement. That the UWA Patents ostensibly identify a binding "hot spot" at position +23+69 and that a POSA could make conservatively modified versions of the sole disclosed example (SEQ ID NO. 195) by shifting position or adding or subtracting nucleobases is not enabling. This same argument was squarely rejected by the Supreme Court in *Amgen*. Amgen similarly claimed its genus was enabled by a "conservative substitution" approach that "requires scientists to: (1) start with an antibody known to perform the described functions; (2) replace select amino acids in the antibody with other amino acids known to have similar properties; and (3) test the resulting antibody to see if it also performs the described functions." *Amgen*, 598 U.S. at 603. The Supreme Court disagreed.

As in *Amgen*, Sarepta "seeks to monopolize an entire class of things defined by their function—every [AO] that both binds to particular areas of the sweet spot of [exon 53] and [induces skipping]." *Id.* at 613. "The record reflects that this class of [AOs] does not include just the [one] that [the UWA Patents have] described by [its base] sequence[], but a 'vast' number of additional [AOs] that it has not." *Id.* (citation omitted). Yet, as the Supreme Court explained in *Amgen*, Sarepta's proffered "approach[]" for enablement "amount[s] to little more than [a] research assignment[]." *Id.* at 614. "It requires scientists to make substitutions to the [base] sequences of [an AO] known to work and then test the resulting [AOs] to see if they do too—an uncertain prospect given the state of the art." *Id.* Such research projects are insufficient to enable the full scope of a broad function genus such as those at issue here.

Nothing in this case justifies a departure from that long-standing precedent. The Court should grant summary judgment that the UWA Patents are not enabled.

VIII. CONCLUSION

For the foregoing reasons, the Court should grant summary judgment in favor of NS and find that the UWA Patents are invalid for lack of written description and enablement.

Dated: December 11, 2023

Respectfully submitted,

MORGAN, LEWIS & BOCKIUS LLP

/s/Amy M. Dudash
Amy M. Dudash (DE Bar No. 5741)
1201 N. Market Street, Suite 2201
Wilmington, Delaware 19801
Telephone: 302.574.3000
Fax: 302.574.3001
amy.dudash@morganlewis.com

Attorneys for Nippon Shinyaku Co., Ltd. and NS Pharma, Inc.

Amanda S. Williamson (admitted *pro hac vice*)
Christopher J. Betti (admitted *pro hac* vice)
Krista V. Venegas (admitted *pro hac* vice)
Wan-Shon Lo (admitted *pro hac* vice)
Maria E. Doukas (admitted *pro hac vice*)
Zachary D. Miller (admitted *pro hac vice*)
Guylaine Haché (admitted *pro hac vice*)
Michael T. Sikora (admitted *pro hac vice*)
110 N. Wacker Drive, Suite 2800
Chicago, IL 60601
Telephone: 312.324.1000
Fax: 312.324.1001
amanda.williamson@morganlewis.com
christopher.betti@morganlewis.com
krista.venegas@morganlewis.com
shon.lo@morganlewis.com
maria.doukas@morganlewis.com
zachary.miller@morganlewis.com
guylaine.hache@morganlewis.com
michael.sikora@morganlewis.com

Alison P. Patitucci (admitted *pro hac vice*)
2222 Market Street
Philadelphia, PA 19103
Telephone: 215.693.5000
Fax: 215.963.5001
salison.patitucci@morganlewis.com

CERTIFICATE OF SERVICE

The undersigned certifies that on December 11, 2023, a copy of the foregoing, which was filed under seal, was served via electronic mail on the following counsel of record:

William B. Raich
Michael J. Flibbert
John M. Williamson
Yoonhee Kim
Yoonjin Lee
FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, LLP
901 New York Avenue, NW
Washington, DC 20001-4413
(202) 408-4000
william.raich@finnegan.com
michael.flibbert@finnegan.com
john.williamson@finnegan.com
yoonhee.kim@finnegan.com
yoonjin.lee@finnegan.com

Charles E. Lipsey
J. Derek McCorquindale
Ryan P. O'Quinn
L. Scott Burwell
1875 Explorer Street, Suite 800
Reston, VA 20190-6023
(571) 203-2700 charles.lipsey@finnegan.com
derek.mccorquindale@finnegan.com
ryan.o'quinn@finnegan.com
scott.burwell@finnegan.com

Alissa K. Lipton
Eric J. Lee, Ph.D.
Two Seaport Lane
Boston, MA 02210-2001
(617) 646-1600
alissa.lipton@finnegan.com
eric.lee@finnegan.com

Jack B. Blumenfeld
Megan E. Dellinger
MORRIS, NICHOLS, ARSHT & TUNNELL LLP
1201 North Market Street
P.O. Box 1347
Wilmington, DE 19899
(302) 658-9200
jblumenfeld@morrisnichols.com
mdellinger@morrisnichols.com

Amanda P. Reeves
Anna M. Rathbun
Graham B. Haviland
Jesse Aaron Vella
LATHAM & WATKINS LLP
555 Eleventh Street, NW, Suite 1000 Washington, D.C. 20004
(202) 637-2200
amanda.reeves@lw.com
anna.rathbun@lw.com
graham.haviland@lw.com

/s/ Amy M. Dudash
Amy M. Dudash (DE Bar No. 5741)